DISSERTATION ON

THE STUDY ON

THYROID FUNCTIONS IN CHRONIC LIVER DISEASE

This dissertation is submitted to

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the requirement of the award
for the degree of

M.D BRANCH I

GENERAL MEDICINE

STANLEY MEDICAL COLLEGE,
CHENNAI – 600001
MARCH 2010

CERTIFICATE

This is to certify that this dissertation entitled

'**THYROID FUNCTIONS IN CHRONIC LIVER DISEASE**' submitted by **Dr. S.SRIRAM** to **THE TAMILNADU DR. MGR MEDICAL UNIVERSITY,CHENNAI** is in partial fulfillment of the requirement of the award of M.D degree Branch-I (General Medicine) and is a Bonafide Research work carried out by him under direct supervision and guidance

Signature of the Unit Chief

Signature of the HOD

Signature of the Dean

DECLARATION

I solemnly declare that the dissertation titled, **'THYROID FUNCTIONS IN CHRONIC LIVER DISEASE'** was done by me at Stanley Medical College and Hospital during 2007 – 2010 under the guidance and supervision of my Unit Chief **Prof. Dr.A.GOWRISHANKAR.,M.D.**

The dissertation is submitted to **THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY** towards the partial fulfillment of requirement for the award of **M.D. Degree (Branch I) in General Medicine**.

Place:

Date:

DR.S.SRIRAM

ACKNOWLEDGEMENT

I owe my thanks to the Dean, Stanley Medical College and Hospital **Dr.A.Priya M.S, D.O**, for allowing me to avail the facilities needed for this study.

I have great pleasure in expressing my gratitude and respect for **Prof.Dr.S.Ramasamy,M.D.,** Professor and Head of the Department of Medicine, Stanley Medical College and Hospital for permitting me to do the study and for his encouragement.

I am extremely thankful to my respected teacher and unit chief **Prof.Dr.A.Gowrishankar M.D**., Professor of medicine , for his guidance and encouragement without which this would not have been possible.

I am extremely thankful to my Assistant Professors **Dr.Nalini Kumaravelu M.D.,** and **Dr.S.Chadrasekar M.D.,** for their valuable guidance and constant encouragement.

I am extremely thankful to the hospital laboratory and its staff members for their immense help in conducting the study.

Finally, I would like to thank my colleagues who offered valuable help to me during the study, and the patients without whose patience, this study would not have been possible.

CONTENTS

INTRODUCTION

INTRODUCTION

Thyroxine and tri-iodothyronine are essential for normal organ growth, development and function. These hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function. The liver plays an important role in thyroid hormone metabolism being involved in their conjugation, excretion, peripheral deiodination and in the synthesis of thyroid binding globulin. Thyroid dysfunction may perturb liver function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs.

Although almost all patients with liver disease are clinically euthyroid, some abnormalities in the circulating hormone concentrations have been shown in previous studies. These data, however, are still controversial as the discrepant results reported may depend on the different analytical methods used as well as different groups of patients investigated.

The total and free thyroxine have been reported as normal, increased or decreased in various liver diseases; abnormalities in thyroxine binding globulin

serum concentration and a reduced thyroid hormone binding capacity, perhaps because of a hypothetical circulating inhibitor, have also been reported. Moreover, total and free triiodothyronine concentration are often decreased, sometimes profoundly and their levels correlate well with severity of liver dysfunction. In order to further evaluate the thyroid function in liver disease, this study measures T3, T4, FT3, FT4 serum levels in patients with chronic liver disease

AIM OF THE STUDY

AIM OF THE STUDY

To evaluate the following :

1. thyroid functions in patients with chronic liver disease

2. To assess the severity of liver dysfunction in relation with interpretation of thyroid functions

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The relationship between the thyroid gland and the liver

Thyroxine and tri-iodothyronine are essential for normal organ growth, development and function. These hormones regulate the basal metabolic rate of all cells, including hepatocytes, and thereby modulate hepatic function; the liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effects. Thyroid dysfunction may perturb liver function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs

Intracellular signaling

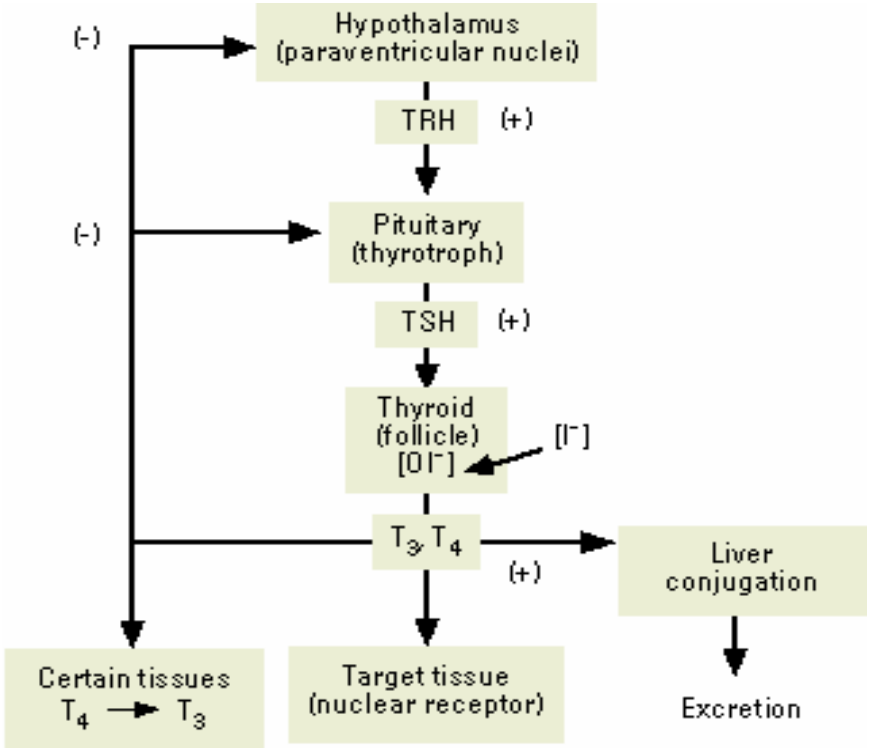
The thyroid gland secretes two iodine containing amine hormones derived from the amino acid tyrosine, L-thyroxine (T_4) and 3,5,3'-L-tri-iodothyronine (T_3). Free T_3 and T_4 enter all cells through the plasma membrane and bind to a nuclear T_3 receptor.

The thyroid receptor is part of the nuclear super family group of receptors (retinoic acid, retinoid X, vitamin D and peroxisome proliferator receptor).These receptors all possess six similar domains, two of which are a ligand-binding region and a central region that constitutively binds to DNA.

The main function of the thyroid receptor is to act as a ligand-activated transcription factor that regulates target gene expression directly through DNA response elements (thyroid response elements).

However, an important property of these receptors is that they bind thyroid response elements constitutively, independent of ligand occupancy.

REGULATION OF THYROID HORMONES



Thyroid hormone metabolism

The thyroid gland secretes 110 nmol of thyroxine and 10 nmol of tri-iodothyronine each day. Tri-iodothyronine has a ten times greater affinity and ten times greater efficacy than thyroxine for the nuclear receptor, thus even though thyroxine is quantitatively secreted at much higher levels, it should be regarded as a pro-hormone that requires deiodination and conversion to T_3 to become biologically active. There are three groups of enzymes that regulate thyroid hormone metabolism, forming part of the iodothyronine seleno-deiodinase enzyme system. They are responsible for the activation of T_4 to T_3, inactivation of T_4 to rT_3 and the conversion of rT_3 and T_3 to T_2

Peripheral conversion of thyroid hormones

The conversion of T_4 to T_3 in extra thyroidal tissue occurs through a rapidly equilibrating pool. The type 1 deiodinase is mainly found in the liver and kidney, and accounts for approximately 30–40% of extra thyroidal production of T_3 (12 nmol). The type 2 deiodinase is found in the pituitary, the CNS, and skeletal muscle and contributes 60–70% of the extra thyroidal production of T_3 (30 nmol). Although this enzyme system performs similar actions to the type 1 de-iodinase activity group of enzymes, its kinetics, regulation and susceptibility to propylthiouracil are different.

Although both the type 1 de-iodinase and type2 de-iodinase system can also inactivate T_4 and T_3, the major inactivator is the type 3 deiodinase system, which primarily exhibits inner-ring deiodination (unlike the other systems). It is found in the liver, skin and CNS, where it catalyses the conversion of T_4 to rT_3 and T_3 to T_2, both inactive metabolites; it also converts rT_3 to rT_2. This enzyme system is also expressed in placenta, where it protects the fetus from maternal thyroid hormones.

In addition to the central role in deiodination to activate and deactivate thyroid hormones, the liver performs specific functions relating to thyroid hormone transport and metabolism.

The liver extracts 5–10% of plasma T_4 during a single passage, as shown by studies using [^{131}I]T_4. This value is much higher than can be accounted for by the amount of free T_4 delivered to the liver, indicating that a substantial amount of bound T_4 is available for uptake. An active stereo-specific transport mechanism has been identified for transporting T_4 and T_3 across the hepatocyte membrane. The intracellular concentrations of the free hormone are higher than the plasma levels, and the process is energy-dependent

The liver synthesizes a number of plasma proteins that bind the lipophilic thyroid hormones and thereby provide a large, rapidly exchangeable pool of circulating hormone. The thyroid hormones are >99% bound to thyroxine-binding globulin, thyroxine-binding prealbumin and albumin in plasma. The free hormone component within plasma is in equilibrium with the protein-bound hormone, and it is this free fraction which accounts for the hormone's biological activities. The plasma concentrations of free T_4 and T_3 are at a steady concentration, so that the tissues are exposed to the same concentrations of the free hormone. However, the free hormone concentrations in different tissues vary according to the transport and deiodinase activity within specific tissues.

Thus tissue thyroid status depends not only on thyroxine secretion but also on normal thyroid hormone metabolism, delivery of T_3 to nuclear receptors and on receptor distribution and function. Normal thyroid function, which is essential for normal growth, development and the regulation of energy metabolism within cells, is dependent on a normally functioning thyroid and liver axis

Thyroid metabolism in chronic illness

In most chronic illness, defects arise in thyroid hormone metabolism, resulting in the sick euthyroid syndrome. This is characterized by a normal total T_4, normal/high free T_4, low total T_3, low free T_3 and an elevated rT_3. These changes reflect a reduction in type 1 de-iodinase activity, an increase in type 3 de-iodinase activity and changes in the plasma concentration of thyroid-binding proteins and free fatty acids (which displace thyroid hormones from binding proteins). There are also non-thyroidal influences on the hypothalamic-pituitary-thyroid axis, e.g. cortisol inhibiting TSH secretion

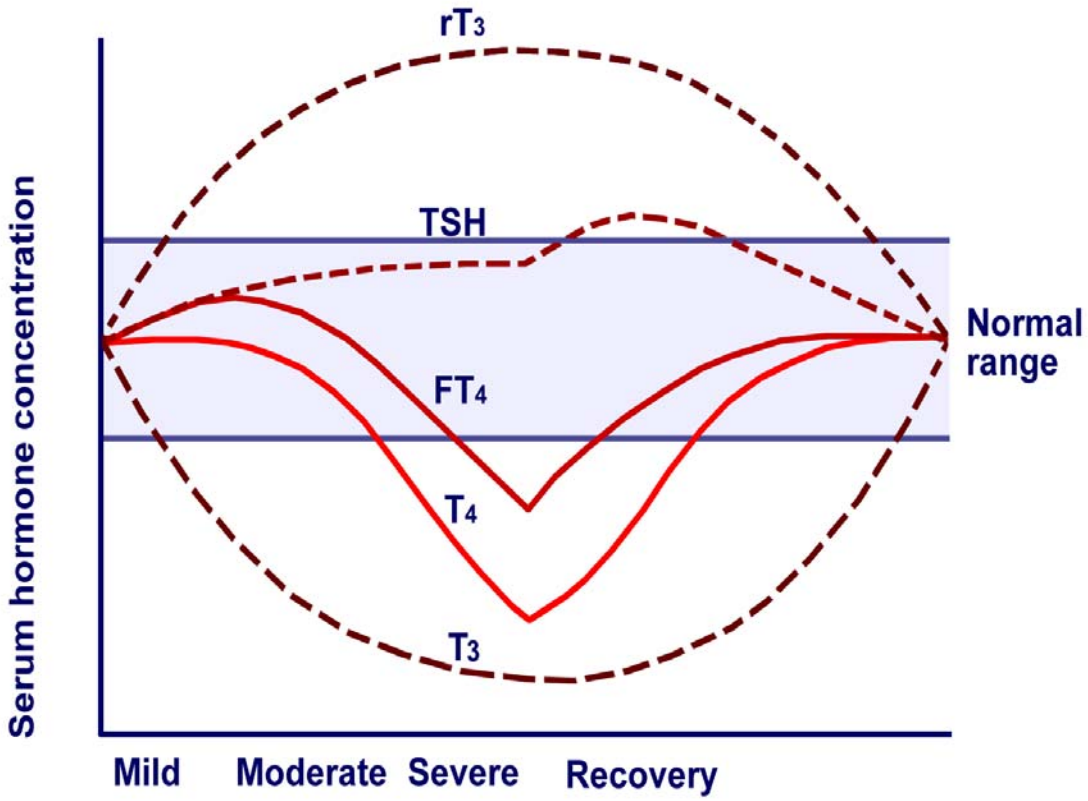
It has been suggested that this syndrome may confer a survival advantage, which adapts an organism to chronic illness by reducing the basal metabolic rate within cells and thereby reducing caloric requirements. These changes in thyroid function test results are observed in most of the acute and chronic illnesses.

Examples of illness include the following:

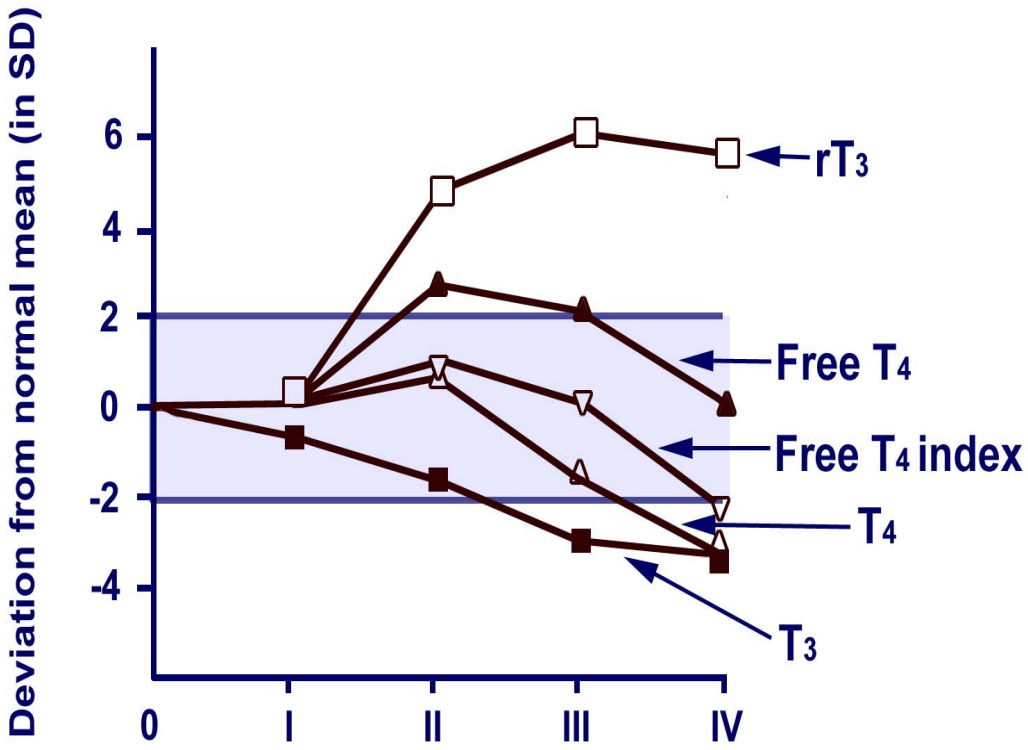
- Gastrointestinal diseases
- Pulmonary diseases
- Cardiovascular diseases
- Renal diseases

- Infiltrative and metabolic disorders
- Inflammatory conditions
- Myocardial infarction
- Starvation
- Sepsis
- Burns
- Trauma
- Surgery
- Malignancy
- Bone marrow transplantation

<u>Fig I</u> - Euthyroid sick syndrome - Relationship between serum thyroid hormone concentrations and severity of nonthyroidal illness



<u>Fig II</u> - Euthyroid sick syndrome. Relationship between severity and duration of nonthyroidal illness (NTI) and thyroid hormone levels.



Pathophysiology

Proposed mechanisms explaining abnormalities in thyroid hormone levels

- **Accuracy of test assays in nonthyroidal illness**

Abnormalities of thyroid function test results might represent test artifacts or true abnormalities. According to one proposition, the assays would indicate reference range thyroid hormone levels in the blood if appropriate tests were applied.

Inhibition of thyroid hormone binding to thyroid-binding proteins and tissues

Serum thyroid hormone abnormalities are due to inhibition of thyroid hormone binding to proteins, thus preventing tests from appropriately reflecting free hormone levels. This binding inhibitor can be present both in the serum and in body tissues and might inhibit uptake of thyroid hormones by cells or prevent binding to nuclear T3 receptors, thus inhibiting the action of the hormone. This inhibitor is associated with the nonesterified fatty acid (NEFA) fraction in the serum.

Contrary to this proposition, substantial evidence indicates that, in an in vivo state, the levels of binding inhibitors do not reach levels sufficient to influence the

circulating levels of free T4, even in patients who are severely ill. Also, some studies have failed to demonstrate an existing binding inhibitor.

- **Cytokines:**

Cytokines are thought to play a role in NTI—particularly interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-alpha, and interferon-beta. Cytokines are thought to affect the hypothalamus, the pituitary, or other tissues, inhibiting production of TSH, thyroid-releasing hormone (TRH), thyroglobulin, T3, and thyroid-binding globulins. Cytokines are also thought to decrease the activity of type I deiodinase and to decrease the binding capacity of T3 nuclear receptors.

- **Deiodination**

Peripheral deiodination of T4 to T3 is impaired, largely secondary to decreased activity of type I deiodinase enzyme, which deiodinates T4 to T3. Diminished enzyme activity accounts for decreased deiodination of T4 to T3.

An alternative explanation is that reduced tissue uptake of T4 secondary to deficiency of cytosolic cofactors (e.g, nicotinamide adenine dinucleotide phosphate [NADPH], glutathione) results in decreased substrate for type I deiodinase enzyme. Type I deiodinase is a selenoprotein; because selenium deficiency is

common in critically ill patients, some propose that selenium deficiency may contribute to type I deiodinase malfunction.

Cytokines (e.g, IL-1 beta, TNF-alpha, interferon-gamma) decrease type I deiodinase messenger RNA (mRNA) in vitro. Type I deiodinase does not exist in the pituitary, where T3 levels are within the reference range, because of enhanced local deiodination. This indicates that an enhancement of intrapituitary T4 to T3 conversion exists due to pituitary-specific and brain-specific type II deiodinase.

- **Inhibition of thyroid-releasing hormone and thyroid-stimulating hormone secretion:**

Cytokines, cortisol, and leptin, as well as changes in brain thyroid hormone metabolism, affect inhibition and secretion of TRH and TSH.

- **Inhibition of plasma membrane transport of iodothyronines:**

Serum factors, such as bilirubin, NEFA, furanoic acid, hippuric acid, and indoxyl sulphate, which are present in various Non Thyroidal Illness (NTIs), have been shown to inhibit transport of thyroid hormones.

- **Thyroxine-binding globulin decrease and desialation:**

T4-binding globulin (TBG) is a member of the serine protease inhibitors. Diminished T4 in NTI has been proposed to be due to low TBG caused by protease cleavage at inflammatory sites in acute inflammatory conditions. One other hypothesis for the cause of disproportionately low serum T4 concentrations in patients with NTI is the presence of abnormal serum binding due to desialation of TBG.

The effects of nonthyroidal illness :

- **Triiodothyronine and reverse triiodothyronine**

In healthy people, 20% of T3 production comes from thyroidal secretion and 80% from peripheral deiodination from T4. In NTI, thyroidal production of T3 is normal, but the peripheral production of T3 is decreased. The fractional rate of transport of T3 to tissues is unaltered. Production of T3 is decreased, but its clearance is unchanged. Production of rT3 is unchanged, while its clearance is diminished.

In rat hepatocytes, rT3 and T4 have been demonstrated to be transported in the same mechanism, which implies that a diminished transport of rT3 to the liver would accompany inhibition of transport of T4 to the liver (e.g., as in during

calorie deprivation). Because the liver is the main site of disposal of T3, this leads to a diminished metabolic clearance rate of rT3 and T4.

Another explanation could be reduced 5'-deiodinase tissue activity, resulting in decreased T3 production from T4 and reduced breakdown of rT3. The decreased production of T3 during early and late starvation has been explained as either a diminished activity of the enzyme (deiodinase) itself or a deficiency of cytosolic cofactors, such as NADPH or glutathione.

Specific deiodinative enzymes, 3 of which have been identified, affect deiodination of iodothyronines. Type I deiodinase is present in the liver, kidney, and thyroid and affects both 5 and 5' deiodination of T3. Type II deiodinase is present in the brain, pituitary, and brown adipose tissue and is active only in 5' deiodination. Type III deiodinase is found particularly in the brain, skin, and placenta, and it deiodinates iodothyronines at the 5 locations.

Both type II and type III enzymes are insensitive to 6-propylthiouracil (PTU). Alterations of serum thyroid hormone parameters in cases of calorie deprivation exhibit similarities to the changes observed in NTI. Fasted animals had decreased 5'-deiodinase activity. The activity of type I deiodinase is inhibited by 6-PTU. Because it is a selenoprotein and selenium deficiency is common in critically ill patients, selenium deficiency also may contribute to its malfunction.

Cytokines, such as IL-1 beta, TNF-alpha, and interferon-gamma, decrease type I deiodinase mRNA in vitro. Infusion of TNF-alpha decreases serum T3 and increases rT3. Soluble TNF-alpha, soluble TNF-alpha receptor, soluble IL-2 receptor antagonist, and IL-6 are inversely correlated with serum T3 levels. The elevations of soluble TNF-alpha receptor and IL-6 were independent determinants of serum T3 and accounted for 35% and 14%, respectively, of the change in T3.

These cytokine changes can be concluded to occur concomitantly with changes in T3 and may play a pathogenic role through mechanisms that are not clearly defined. The increase of endogenous cortisol during illness apparently is not involved in inhibition of type I deiodinase.

Using an adenovirus model in mice hepatocyte primary cultures, it was demonstrated that forced expression of steroid receptor co-activator 1 (SRC-1) prevented the cytokine induced inhibition of type 1 deiodinase activity, suggesting the involvement of receptor co-activators in the nonthyroidal illness.

- **Free triiodothyronine**:

Most studies have found free T3 hormones to be depressed.

- **Thyroxine**

The decrease in the T4 binding of TBG has been used as an explanation for the low plasma T4 concentration in patients with NTI. The existence of a binding inhibitor could explain the observed alterations in T4 and free T4 fraction. TBG levels usually are within the reference range in patients with NTI and are somewhat lower in critically ill patients with low serum T4. Low TBG levels can be explained, according to some proposals, by rapid protease cleavage at inflammatory sites, particularly in acute inflammatory states (in which the decrease in TBG is too rapid to be accounted for by inhibition of synthesis).

In patients with NTI, serum T4 concentration has been demonstrated to be low because much of the circulating TBG in these patients is desialated. In NTI, the fractional rate of T4 transport from serum to tissues is reduced to 50% of the reference range value. This decrement in fractional rate of T4 transport is not related to the serum levels of total or free T4. Because in illness the reduction in the fractional rate of T4 transport from serum to tissues cannot be attributed to alterations in serum T4 binding, consider other causes such as an impairment of transport into tissues.

In nonuremic critical illness, it has been demonstrated that elevated bilirubin or elevated NEFA and low albumin concentration may be at least

partially responsible for the T4 transport inhibition in T3-producing tissues (e.g, the liver).

A correlation exists between the probability of death and the levels of total T4. When serum T4 levels drop below 4 mcg/dL, the probability of death is about 50%; with serum T4 levels below 2 mcg/dL, the probability of death reaches 80%.

- **Free thyroxine**

Evaluating thyroid function in patients with NTI has considerable challenges. No consensus exists as to whether free T4 levels are within the reference range, low, or high. Free T4 is believed to represent the hormone available to tissues.

Measurement of total serum T4 has only limited value because nearly all (99.97%) of the circulating T4 is bound to TBG, T4-binding prealbumin (TBPA), and albumin. The rest of the circulating T4 (0.2-0.03%) is free T4. The circulating concentration of these binding proteins is understood to affect the total T4 concentration without necessarily changing the amount of free T4. Usually, TBG levels are within the reference range in patients with NTI and somewhat lower in critically ill patients with low serum T4.

Decreased concentrations of one or more of the binding proteins would explain low levels of total T4 but does not explain a significant increase in free T4 fraction, which some patients with NTI exhibit.

Various explanations for the existence of inhibitors of T4 binding have been reported. Although low levels of TBPA and albumin may occur in patients with NTI, even complete inhibition of T4 binding to these proteins has been demonstrated to produce only about a 30% increase in free T4 fraction. Because free T4 fraction is increased above this level in many patients, other factors must be present.

The observations of reduced total T4 and free T4 have been explained alternatively as either a fall in TBG levels or an inhibition of thyroid hormone binding to TBG. Some studies have shown a decrease in the T4 binding of TBG, which has been used as an explanation for the low plasma T4 concentration and, perhaps, the high free T4 fractions, in patients with NTI. Other studies postulate the existence of a binding inhibitor that could explain the observed alterations in free T4 fraction.

The inhibitor also has been demonstrated to interfere with the binding of iodothyronines to solid matrices, thus interfering with the T3 resin uptake and explaining the low FTI found in patients with NTI. The inhibitor appears to be

extractable with ether and was associated with the NEFA fraction in the serum. Furthermore, the extracted inhibitor from sera of patients with NTI reduced conversion of T4 to T3 in rat liver homogenates. The inhibitor could be extracted from extrathyroidal tissues as well.

The addition of NEFA to normal serum is able to raise the free T4 fraction only if total NEFA concentration is higher than 3 millimoles in normal serum, representing a NEFA-to-albumin molar ratio greater than 5:1. Because this high NEFA-to-albumin ratio is not reached even in severely ill patients, NEFA is unlikely to influence the circulating free T4 concentration in vivo. Inhibitors of binding were also observed during equilibrium dialysis assay in patients treated with heparin. This is due to an in vitro artifact that is not present in vivo.

Cytokines also can elevate free T4. When TNF-alpha was infused, it was observed that free T4 could elevate transiently in association with a significant rise in free fatty acids. However, other studies question the role of NEFA inhibition or whether any thyroid hormone–binding inhibitor exists at all.

- **Thyroid hormone receptor expression and DNA binding:**

In experimental mouse liver models, infection decreased thyroid hormone receptor (TR) expression as well as retinoid X receptor (RXR)–TR DNA binding.

TR-alpha and TR-beta protein levels were both decreased when lipopolysaccharide was administered, particularly at 16 hours. Lipopolysaccharide exposure was also shown to reduce RXR protein levels in the liver.

- **Thyroid-stimulating hormone and thyroid-releasing hormone**

Some patients with Non Thyroidal Illness have slightly elevated serum TSH, which is thought to have reduced biological activity. After recovery from severe Non Thyroidal Illness, transient elevation of TSH to above-normal limits commonly occurs. Some authors interpret this TSH elevation as a sign of recovery from a hypothyroid state. Despite the distortion of TSH in some euthyroid patients with Non Thyroid Illness, patients with Non Thyroidal Illness who have significant elevation of TSH usually have underlying primary hypothyroidism.

Responsiveness of the pituitary to TRH during Non Thyroidal Illness varies; some patients respond normally, while many have a less-than-normal response. Normal responsiveness in the presence of low TSH may suggest that a hypothalamic abnormality is causing the low TSH and low T4. The down-regulation at the hypothalamus-pituitary level provides an explanation for the decreased sensitivity of TSH secretion to low serum T3 and T4 concentrations in patients with Non Thyroidal Illness. A diminution, or loss, of the diurnal rhythm of

TSH also occurs, and some studies have produced evidence for a reduction of TSH glycosylation with lower TSH bioactivity.

That TSH is not elevated in the presence of low T4 indicates that the patients are not hypothyroid. Diminished release of TRH also is thought perhaps to result in low TSH and, thus, low output of thyroid hormones by the thyroid. Low TRH mRNA in hypothalamic paraventricular nuclei also has been demonstrated.

The role of cytokines, especially IL-1 beta, in the activity of the hypothalamic-pituitary-adrenal axis is well known. Cytokines also affect TRH in rats. IL-1 beta decreases the release of TSH in cultured rat anterior pituitary cells, but the role of TNF-alpha on TSH release is disputed. IL-6 decreases TSH secretion. In rodents, leptin has been demonstrated as a major mediator of changes in hypothalamic-pituitary-thyroid function during fasting. However, TSH secretion and thyroid gland function are less affected during Non Thyroidal Illness in humans than they are in animals.

The role of leptin in patients with Non Thyroidal Illness is unclear. Leptin concentrations often are elevated during critical illness and increase acutely in response to administration of TNF-alpha or IL-1; however, the leptin increase is not related to changes in serum T3 and T4 concentrations.

Thyroid abnormalities in liver disease

In the different types of liver disease**,** similar processes may occur to those seen in the sick euthyroid syndrome, but in addition a number of changes specific to the type or stage of liver disease is also found**.**

Cirrhosis

The most consistent thyroid hormone profile in patients with cirrhosis are a low total and free T_3 and an elevated rT_3, similar changes to those in the sick euthyroid syndrome, probably reflecting a reduced deiodinase type 1 activity, resulting in reduced conversion of T_4 to T_3. This results in an increase in conversion of T_4 to rT_3 by the deiodanase type 3 system, and an increase in the rT_3 to T_3 ratio.

The plasma T_3:rT_3 ratio has a negative correlation with the severity of cirrhosis when assessed in non-alcoholic cirrhotics. Since T_3 and rT_3 bind to the same plasma proteins, the T_3/rT_3 ratio provides a parameter of liver function that is largely independent of protein binding. Both the T_3/rT_3 ratio and free T_3 levels in plasma thus provide a correlate of liver function in cirrhosis, and are of prognostic value, albeit seldom used.

The low total and free T_3 levels may be regarded as an adaptive hypothyroid state that serves to reduce the basal metabolic rate within hepatocytes and preserve liver function and total body protein stores. Indeed, a recent study in cirrhotic patients showed that the onset of hypothyroidism from intrinsic thyroid disease of various etiologies during cirrhosis resulted in a biochemical improvement in liver function (e.g. coagulation profiles) as compared to cirrhotic controls. Hypothyroidism has also been associated with lesser degrees of decompensation in cirrhosis. Controlled induction of hypothyroidism might therefore be beneficial in cirrhotic patients, but further studies are required to test this hypothesis.

Acute hepatitis and acute liver failure

In acute hepatitis of mild or moderate severity, patients have elevated serum levels of total T_4, due to increased thyroid-binding globulin, which is synthesized as an acute-phase reactant, but normal levels of free T_4. In more severe cases with impending liver failure, the data is variable, and low total T_4 levels may reflect reduced hepatocellular synthesis of thyroid-binding globulin.

Serum T_3 levels are extremely variable, but the free T_3:T_4 ratio correlates negatively with the severity of the liver disease and has prognostic value. Again this probably reflects diminished type 1 deiodinase activity, resulting in a reduced conversion of T_4 to T_3; in general, however, these patients are clinically euthyroid.

Some series have described patients with acute hepatic failure (especially viral hepatitis) as having goiters that resolved with improvement in liver function.

Specific forms of chronic liver disease

In patients with chronic hepatitis associated with primary biliary cirrhosis (PBC) or chronic autoimmune hepatitis, there is an increased prevalence of autoimmune thyroid disease. Thus abnormalities may arise from thyroid gland dysfunction or as a consequence of the liver disease. Autoimmune hypothyroidism is a prominent feature in PBC, occurring in 10–25% of patients. There is often an increase in total T_4 in PBC, due to an increase in thyroid-binding globulin levels, and this may mask hypothyroidism, emphasizing the need to perform a free T_4 and TSH assay. Anti-thyroid microsomal antibodies are common in PBC (34%), as are anti-thyroglobulin antibodies (20%).Thyroid dysfunction may precede or follow the diagnosis of PBC. In autoimmune hepatitis, both Grave's disease (6%) and autoimmune hypothyroidism (12%) are relatively common. Primary sclerosing cholangitis is associated with an increased incidence of Hashimoto's thyroiditis, Graves's disease and Riedel's thyroiditis.

In patients with chronic hepatitis who do not have co-existing autoimmune liver and thyroid disease, total T_4, total T_3, thyroxine-binding globulin levels are

often increased, but TSH and free T_4 levels are usually normal, and patients are clinically euthyroid.

Currently the treatment of viral hepatitis with alpha interferon has added another dimension to the abnormalities of thyroid function seen in chronic liver diseases. In different studies assessing patients treated with alpha interferon for hepatitis C, 2.5–10% developed thyroid dysfunction, with both thyrotoxicosis (due to acute thyroiditis) and hypothyroidism being observed. Although the reason is not altogether clear, the induction of an autoimmune reaction has been postulated, resulting in the development of anti-thyroid and anti-thyrotrophin receptor antibodies. However, a distinct effect on intrathyroidal organification of iodine has also been suggested.

The risk factors for developing thyroid dysfunction with alpha interferon (which may persist after discontinuation of the drug) are female sex, underlying malignancy, high doses of long duration, combination immunotherapy (especially Il-2), and the presence of anti-thyroid peroxidase antibodies prior to commencing treatment.

It should be noted that interferon therapy causes weakness and muscle aching, and in this setting the myopathy of hypothyroidism may be missed. It is therefore recommended that thyroid function tests (including thyroid antibodies)

are performed prior to therapy, and subsequently monitored at 3–6 month intervals during interferon therapy.

Liver abnormalities in thyroid disease

Hypothyroidism

Hypothyroidism may have features that mimic liver disease (pseudo-liver disease): examples include myalgias, fatigue and muscle cramps in the presence of an elevated aspartate aminotransferase from a myopathy, coma associated with hyperammonaemia in myxoedema coma, and myxoedema ascites.

Hyperthyroidism

Liver injury caused by thyrotoxicosis is relatively common, and can be conveniently divided into hepatitic or cholestatic types.

Hepatitic injury

An increase in the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) is seen, although the majority of these patients showed no other clinical or biochemical features of liver impairment. The mechanism of injury appears to be relative hypoxia in the perivenular regions, due to an increase in hepatic oxygen demand without an appropriate increase in hepatic blood flow

Cholestatic injury

An elevated serum alkaline phosphatase is seen in of patients with thyrotoxicosis

Anti thyroid drugs

Increased serum levels of aspartate aminotransferase and alanine aminotransferase occur in about 30% of patients treated with propylthiouracil. The rise in AST appears to be dose-related, so that AST and ALT levels are highest during the first few weeks of treatment, falling rapidly with a dose reduction

Other thyroid and liver interactions

Physiological

The liver is the major site for cholesterol and triglyceride metabolism, and the thyroid hormones play an integral part in hepatic lipid homeostasis. Thyroid hormones increase the expression of LDL receptors on the hepatocytes, and increase the activity of lipid-lowering liver enzymes, resulting in a reduction in low-density lipoprotein levels. Thyroid hormones also increase the expression of apolipoprotein A1, a major component of high-density lipoprotein.

Pathological

A number of disease processes and drugs can affect both the liver and the

thyroid gland simultaneously. The autoimmune diseases, organ infiltration such as malignancy, amyloid, or in secondary haemachromatosis, drugs like amiodarone, mefloquine, carbamazepine

Recent work investigating the use of tri-iodothyronine as a hepatic growth factor has shown it to be a primary mitogen for the liver in animal models (i.e. it induces hepatocyte proliferation and increases liver mass when administered at high doses in the absence of hepatic injury). The ability to increase liver mass in the absence of liver damage, and to enhance proliferation during compensatory hyperplasia after liver damage, could be therapeutically valuable if applicable to man. More generally, the ability to manipulate liver cell proliferation in vivo may be helpful in designing cell transplantation and gene therapy approaches to liver diseases.

Diagnosis of Thyroid Disease in Euthyroid Sick Syndrome

During starvation and mild illness, a low T_3 concentration, or low T_3 and low T_4 levels in a patient with a low-normal TSH level, is the hallmark of euthyroid sick syndrome. However, nonthyroidal illness may present with a spectrum of abnormalities in thyroid function that may complicate the diagnosis of euthyroid sick syndrome.

Low T_3 levels with normal T_4 and TSH levels are the most common abnormality seen in euthyroid sick syndrome. Serum TSH levels are typically normal or reduced. The TSH levels are normal/subnormal in approximately 80% of patients, and are markedly suppressed (<0.1 µU/mL) in <10% of patients. Thus, in a patient with a systemic illness, low T_4 and T_3 levels and a normal or low-normal TSH level most likely indicate euthyroid sick syndrome.

In the recovery phase of illness, mild elevation of TSH levels can be observed; however, serum level of TSH >30 µU/mL is rarely seen in euthyroid sick syndrome and strongly suggests the diagnosis of primary hypothyroidism. Levels of TSH above 20 µU/mL are found in <3% of patients with nonthyroidal illness.

Differentiation between secondary hypothyroidism (pituitary or hypothalamic) and euthyroid sick syndrome may be difficult. Both conditions present with decreased levels of total T_4, T_3, and TSH. Many chronically ill patients are edematous, have associated infections, or have cardiopulmonary disorders that could easily mask evidence of thyroid disorders. Additional tests, including obtaining basal and/or stimulated cortisol, serum gonadotropin, and prolactin levels may be of help in such cases. If the serum cortisol level is normal or elevated, as would be expected in stressful situations, euthyroid sick syndrome

is probably the cause, rather than pituitary dysfunction. If serum cortisol and gonadotropin levels are low, pituitary dysfunction should be suspected, and treatment with corticosteroids and thyroid hormone supplementation is indicated.

In some instances, it may be difficult to exclude hyperthyroid patients, who may present with suppressed TSH levels and normal T_4 and T_3 levels in the presence of infection or other catabolic illness. Hyperthyroid patients who are chronically ill or malnourished may have hypoproteinemia and low levels of TBG that lower their T_4 and T_3 levels. In such patients, an elevated free-T_4 level and a low or undetectable TSH level will confirm the diagnosis of hyperthyroidism. A previous history of thyroid illness, a history of external radiation, or the presence of goiter and/or a midline neck scar may indicate a primary thyroid condition.

Certain pharmacologic agents may alter the serum concentration of thyroid hormones and should be taken into account in the evaluation of patients with nonthyroidal illness. The concentrations of total T_3, free-T_4, and TSH are reduced in patients treated with dopamine or corticosteroids, due to suppression of pituitary TSH release and/or inhibition of conversion of T_4 to T_3. Levels of total and free-T_4 may be increased in patients treated with amiodarone or iodinated radiocontrast agents. Intravenous or subcutaneous heparin therapy may result in increased free-

T_4 levels, due to in vitro interference with the laboratory assay; however, most such patients remain clinically euthyroid and have normal total T_4 and TSH levels.

It is not prudent to rely solely on a single thyroid test in the evaluation of thyroid function of patients with critical illness. In such patients, a careful assessment of multiple tests may be needed to distinguish patients with euthyroid sick syndrome. In many instances, it is reasonable to delay the final diagnosis for several days to weeks, or after recovery from the acute illness, to determine the correct thyroid status.

Faber J et al kinetic studies of thyroxine, 3,5,3'-triiodothyronine, 3,3,5'-triiodothyronine, 3',5'-diiodothyronine, 3,3'-diiodothyronine, and 3'-monoiodothyronine in patients with liver cirrhosis found that serum T_4, T_3, and 3,3'-T_2 levels were reduced in patients with liver cirrhosis, whereas serum rT_3 and 3',5'-T_2 levels were increased. Serum 3'-T_1 levels were unaltered.

Chopra IJ et al showed alterations in circulating thyroid hormones and thyrotropin in hepatic cirrhosis: evidence for euthyroidism despite subnormal serum triiodothyronine

Nomura S et al showed reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis.

Bermudez F et al observed a high incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease.

Bianchi GP et al measured Thyroid volume at ultrasound in 118 consecutive patients with cirrhosis of different etiology and 48 healthy subjects matched for age and sex. No subjects had evidence of overt thyroid disease. The mean volume was increased by 17% (from 16.0 [SD 5.2] ml in controls to 18.8 [7.6] in cirrhosis; P less than 0.025), and thyroid enlargement (antero-posterior diameter greater than 20 mm) was present in 38% of cases, in the presence of hormone values indicative of low-T3 syndrome. No significant differences in thyroid gland size were observed in relation to the extent of liver dysfunction or to the etiology of liver disease. The prevalence of thyroid nodules was similar in controls and in patients with cirrhosis

M Borzio et al studied thyroid function tests in chronic liver disease and confirmed the existence of several abnormalities of thyroid function tests in patients with chronic liver disease, although showing that euthyroidism is almost always maintained, probably as a result of low-normal FT3 and high-normal FT4.

L'age M, Meinhold H, Wenzel KW, Schleusener H measured Serum levels of TSH, thyroxine-binding globulin (TBG), T4, T3 and reverse T3 (rT3) in 36 patients with fatty liver disease, 11 patients with chronic persistent hepatitis, 17 patients with chronic active hepatitis, and 29 patients with liver cirrhosis. TBG was significantly above normal levels in both groups of chronic hepatitis, the slight concomitant T4 and T3 increase was significant only for T4 in chronic persistent hepatitis. A significant decrease in T4 and T3 concentration was found in fatty liver disease and in hepatic cirrhosis. A shift in T4 conversion to rT3 could exclusively be demonstrated for the group of hepatic cirrhosis, reflected by a significant increase in rT3

Hitomi TAKAHASHI et al studies on changes of Thyroid Hormones in Various Liver Diseases showed usefulness of free Thyroid Hormones as Liver Function Test.

R. MALIK and H. HODGSON studied the relationship between the thyroid gland and the liver and observed that thyroxine and tri-iodothyronine hormones modulate hepatic function; the liver in turn metabolizes the thyroid hormones and regulates their systemic endocrine effects. Thyroid dysfunction may perturb liver

function, liver disease modulates thyroid hormone metabolism, and a variety of systemic diseases affect both organs.

Van Thiel DH et al assayed T4, T3, rT3 and TSH in 134 adult patients evaluated and accepted as potential liver transplant candidates at the University of Pittsburgh from March, 1981 to December, 1983. The subsequent course of these patients was evaluated with respect to the levels of these hormones obtained at the time of acceptance for transplantation. T4 levels were increased significantly while their T3 levels were reduced (both p less than 0.01) in those who survived and were discharged home as compared to either those who died waiting to be transplanted or died following the procedure. As a result, the ratio of T3/T4 was reduced markedly (p less than 0.01) in those who were transplanted and survived as compared to those not transplanted or dying following transplantation

Van Steenbergen W, et al studied thyroid hormones and the hepatic handling of bilirubin and effects of hypothyroidism and hyperthyroidism on the hepatic transport of bilirubin

Malik R et al studied the effects of thyroid hormone on the liver and suggested a novel approach to increase liver mass.

MATERIALS AND METHODS

MATERIALS AND METHODS

SETTING : 40 patients with symptoms, signs with biochemical and radiological evidence of chronic liver disease who were admitted in the general medical ward of Government Stanley Medical College and Hospital were enrolled for this study after prior written and informed consent

The age group of these patients ranged from 25 years to 75 years

PERIOD OF STUDY : JANUARY 2009 – OCTOBER 2009

ETHICAL COMMITTEE APPROVAL : The present study was approved by the ethical committee

CONSENT : Study group thus identified was informed about the nature of the study and willing participants were included in the study after getting written informed consent

SAMPLE POPULATION : 80 Patients – 40 cases and 40 controls

Out of these 40 cases, 30 patients were males and 10 patients were females.

Out of the 30 males, 25 had had alcohol related chronic liver disease and out of the remaining 5, 2 patients had Wilson's disease, 3 had post viral chronic liver disease.

Out of the 10 females, 5 had post viral chronic liver disease, 2 patients had alcoholic liver disease and remaining had cryptogenic cirrhosis.

All subjects were hospitalized because of signs and symptoms of decompensated liver disease.

INCLUSION CRITERIA :

- Patients with symptoms, signs with biochemical and radiological evidence of chronic liver disease
- Those patients willing to participate in the study

EXCLUSION CRITERIA

- Patients with upper gastro intestinal bleeding,
- Patients with acute hepatic encephalopathy
- Patients with renal failure
- Patients on thyroid medications already

Our patients did not show clinical signs or symptoms of thyroid dysfunction and did not receive medications that might have affected the radio immuno assay performed in the study.

As a control group 40 healthy subjects (30 men; 10 women) aged 25 – 75 years, matched for their age, sex was investigated.

All the patients were assessed for the duration of chronic liver disease and were also asked about past history of jaundice, blood transfusion, marital and sexual history and duration of alcoholism (if present).

Physical examination in search of stigmata of chronic liver disease was routinely done in all patients. Ophthalmologic examination was done to look for KF ring. Detailed cardiovascular and neurological examination was done.

Each patients' complete history was recorded in a proforma. Every patient was investigated in the following order after the completion of physical examination

Blood:

Hemoglobin

Total WBC count; Differential count

ESR

Random blood sugar

Blood urea

Serum creatinine

Liver function tests

Ultrasound abdomen and pelvis

Portal vein Doppler

Serum T3, T4, TSH FT3, FT4

Serum T3, T4 was determined by standard radio immuno assay. Serum free T3 (FT3) and free T4 (FT4) were measured by direct radio immuno assay.

Patients were deferred liver biopsy owing to clinical conditions or coagulation abnormalities.

The normal ranges for thyroid functions in our laboratory are as follows:

T3 : 80 – 200 ng / dl

T4 : 4.5 – 12 mcg / dl

FT3 : 2.7 – 6.6 pg / ml

FT4 : 6.3 – 16.4 pg / ml

Blood samples were also collected from 40 control subjects for thyroid and liver function analysis.

All the vital data and blood reports for the study and control group were entered into a master chart and analysed

The statistical analysis was carried out using unpaired t test. Data were expressed with respect to ‘p’ value, mean and standard deviation.

RESULTS

RESULTS

Total no. of patients in the study group : 40

Male : 30

Female : 10

Total no. of controls in the study group : 40

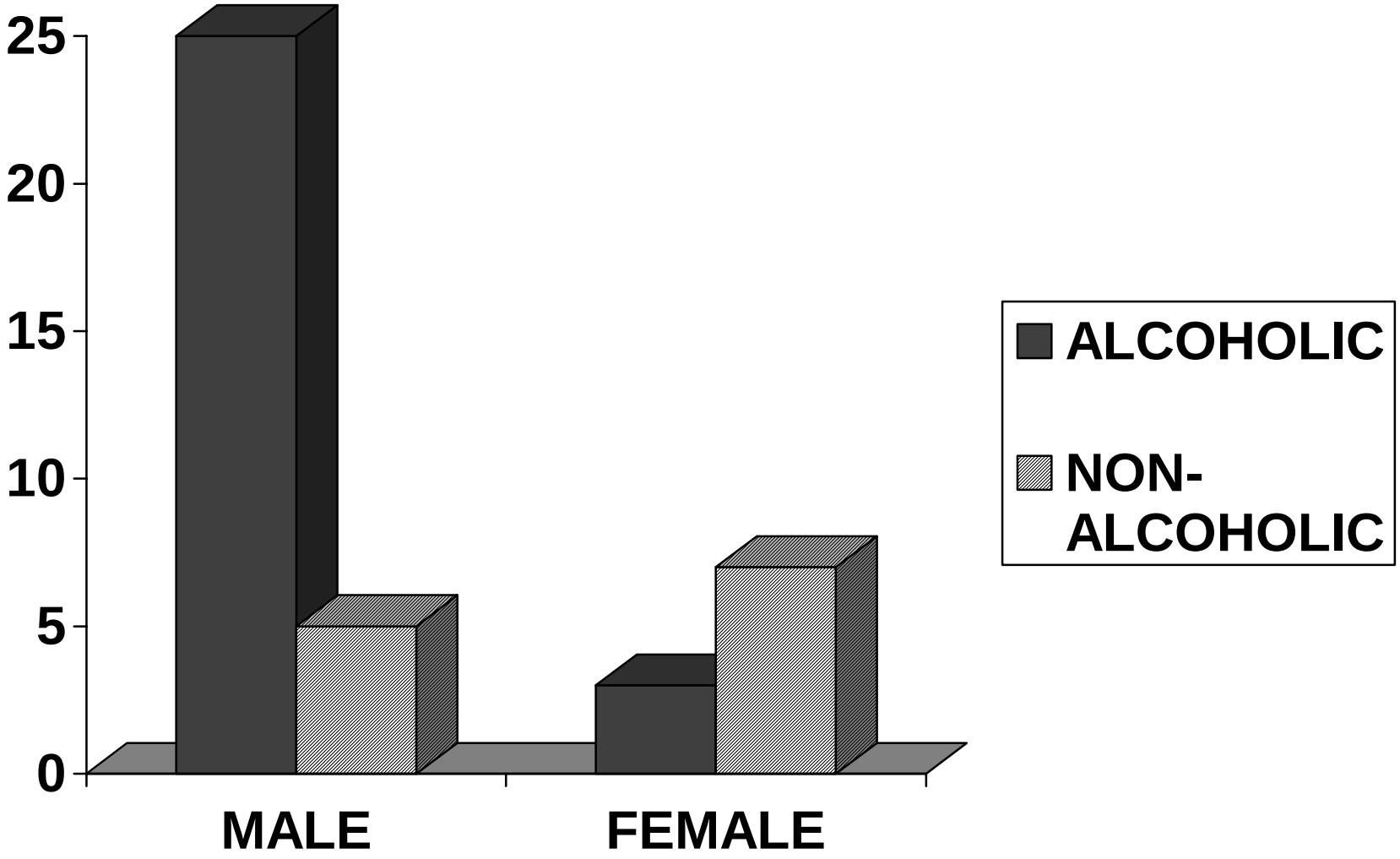
Male : 30

Female : 10

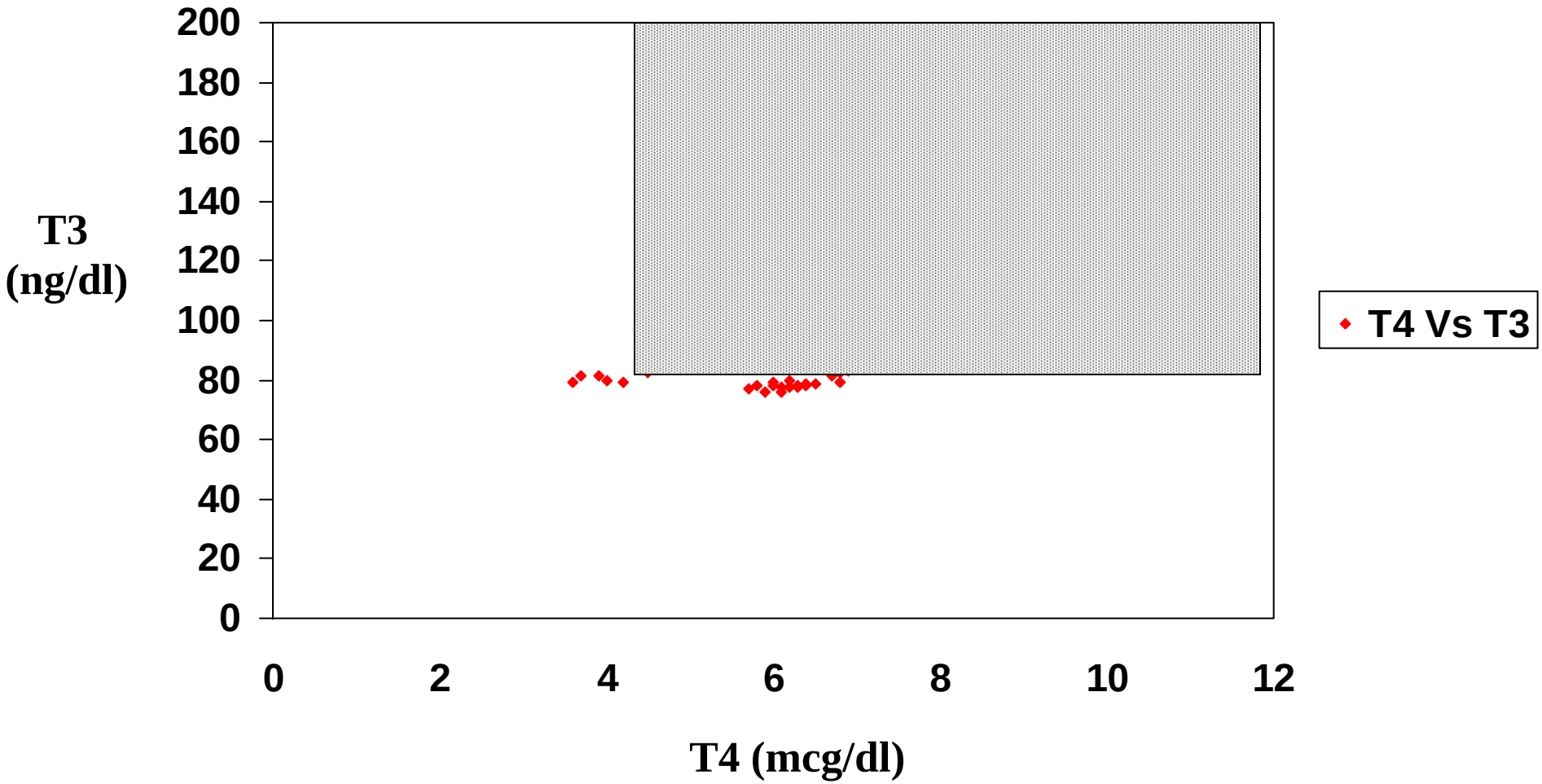
Table I

Age wise distribution of patients in the study group

Age group (in years)	Male	Female
25 - 35	2	3
35 - 45	3	5
45 - 55	20	1
55 - 75	5	1

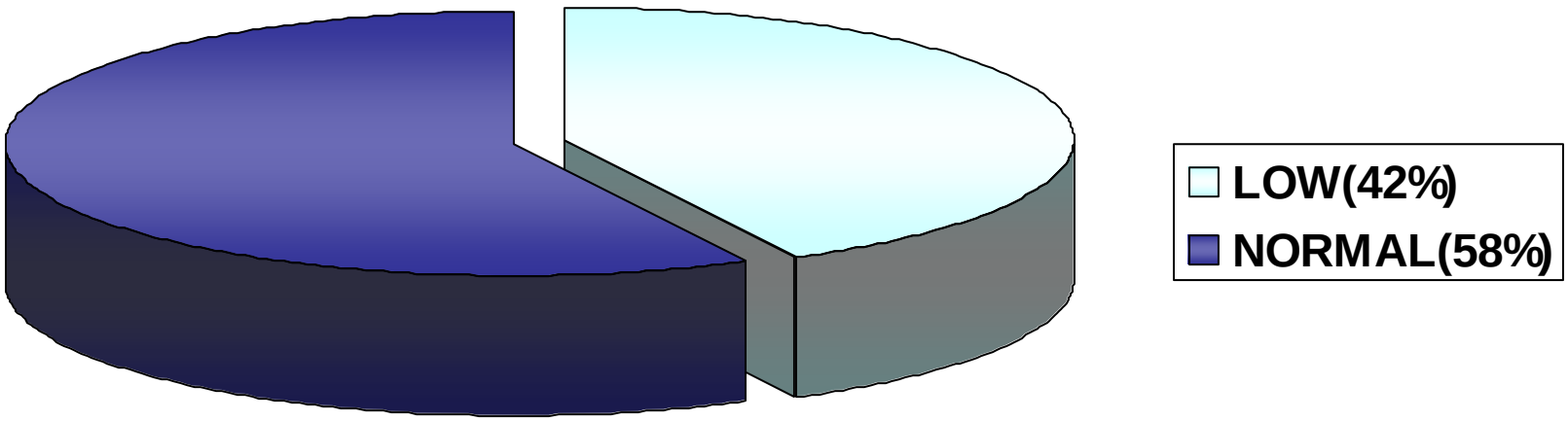

25
20
15
10
5
0
MALE
FEMALE
ALCOHOLIC
NON-
ALCOHOLIC

SCATTER DIAGRAM SHOWING SERUM T4 vs.T3 IN INDIVIDUAL PATIENTS WITH CHRONIC LIVER DISEASE



- zone represents normal values of T3 and T4

SERUM T3 VALUES IN PATIENTS WITH CHRONIC LIVER DISEASE



SERUM T4 VALUES IN PATIENTS WITH CHRONIC LIVER DISEASE

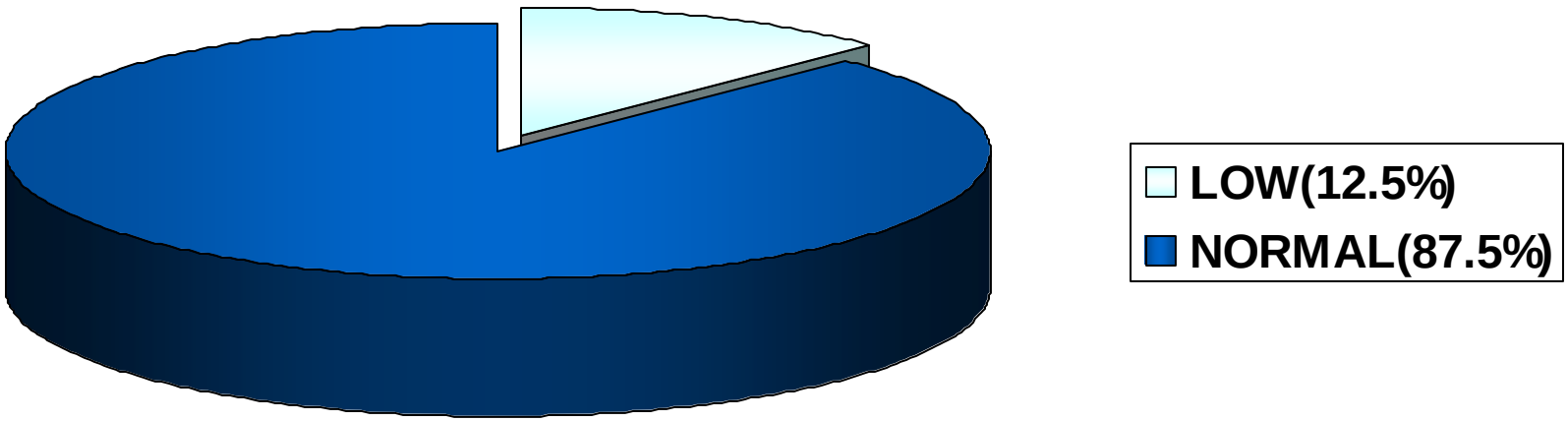


Table II

Clinical diagnosis and etiological factors:

	No. of Patients	Alcoholic	Post viral	Others
Male	30	25	3	2
Female	10	2	5	3

Table III

Biochemical indices of liver function of patients:

SGPT	BILIRUBIN	ALBUMIN	PROTHROMBIN TIME
40 ± 9	2 ± 0.6	2.7 ± 0.1	35 ± 5

Table IV

Indices of thyroid function in patients with chronic liver disease and sex and age matched healthy controls (mean values with standard deviation)

	T3(ng/dl)	T4(mcg/dl)	FT3(pg/ml)	FT4(pg/ml)	TSH(m U/ml)
Cases	84.1 ± 9.6	6.2 ± 1.3	3.7 ± 0.9	11.5 ± 2.6	3.2 ± 0.9
Controls	92.7 ± 8.1	7.1 ± 1.2	4.2 ± 0.7	12.9 ± 2.4	3.7 ± 0.9

INTERPRETATION OF THE VALUES :

- Patients with chronic liver disease showed significantly reduced serum levels of T3.

- 4 patients had low normal levels of FT3.

- 5 patients had low T4 values.

- All patients had normal FT4 and TSH values.

- Simple correlation analysis showed that the serum T3 concentration significantly correlated with serum bilirubin, albumin and prothrombin in chronic liver disease but not with transaminases.

STATISTICAL ANALYSIS :

T3 :

- Out of 40 cases, T3 value ranged from a minimum of 76 to maximum of 112.2 ng/dl
- Mean value of T3 among cases was 84.1 ng/dl
- Standard deviation of T3 among cases was ± 9.6
- Out of 40 controls, T3 value ranged from a minimum of 82 to maximum of 118.0 ng/dl
- Mean value of T3 among controls was 92.7 ng/dl
- Standard deviation of T3 among cases was ± 8.1

'p' value calculated for T3 is ≤0.001 which is statistically significant.

T4 :

- Out of 40 cases, T4 value ranged from a minimum of 3.6 to maximum of 9.7 mcg/dl
- Mean value of T4 among cases was 6.2 mcg/dl
- Standard deviation of T4 among cases was ± 1.3

- Out of 40 controls, T4 value ranged from a minimum of 4.6 to maximum of 10.2 mcg /dl
- Mean value of T4 among controls was 7.1 mcg / dl
- Standard deviation of T4 among cases was ± 1.2

'p' value calculated for T4 is <u>0.0013</u> which is statistically significant.

<u>Free T3:</u>

- Out of 40 cases, FT3 value ranged from a minimum of 2.55 to maximum of 6.1 pg/ml
- Mean value of FT3 among cases was 3.7pg/ml
- Standard deviation of FT3 among cases was ± 0.9
- Out of 40 controls, FT3 value ranged from a minimum of 2.8 to maximum of 6.4 pg/ml
- Mean value of FT3 among controls was 4.2 pg/ml
- Standard deviation of FT3 among cases was ± 0.7
- **'p' value calculated for FT3 is <u>0.0042</u> which is statistically significant**

<u>FT4 :</u>

- Out of 40 cases, FT4 value ranged from a minimum of 6.3 to maximum of 16.4 pg/ml

- Mean value of FT4 among cases was 11.5 pg/ml
- Standard deviation of FT4 among cases was ± 2.6
- Out of 40 controls, FT4 value ranged from a minimum of 8.75 to maximum of 16.4 pg/ml
- Mean value of FT4 among controls was 12.9 pg/ml
- Standard deviation of FT4 among cases was ± 2.4
- **'p' value calculated for FT4 is <u>0.008</u> which is statistically significant**

<u>TSH :</u>

- Out of 40 cases, TSH value ranged from a minimum of 1.73 to maximum of 5.4 mU/ml
- Mean value of TSH among cases was 3.2 mU/ml
- Standard deviation of TSH among cases was ± 0.9
- Out of 40 controls, TSH value ranged from a minimum of 2.0 to maximum of 5.5 mU /ml
- Mean value of TSH among controls was 3.7 mU/ml
- Standard deviation of T4 among cases was ± 0.9

'p' value calculated for TSH is <u>0.014</u> which is statistically significant.

DISCUSSION

DISCUSSION

The existence of low T3 syndrome i.e., low total T3 with normal total T4 in the absence of clinical hypothyroidism has been frequently reported in patients with chronic liver disease and it has been shown to depend on impaired liver conversion of T4 to T3.

The liver plays an important role in thyroid hormone metabolism being involved in their conjugation, excretion, peripheral deiodination and in the synthesis of thyroid binding globulin.

This study confirms a highly significant decrease in T3 serum concentration in liver disease, the lowest values correlate with sever disease

In a large group of alcoholic patients Israel et al reported a significant correlation between serum T3 concentration and severity of liver dysfunction as well as progressive T3 increase in those subjects eventually displaying favourable outcome suggesting that T3 concentration in patients with advanced liver disease may be considered as helpful prognostic indicator.

This study found a good correlation between T3 concentration and serum albumin, bilirubin, prothrombin time while no correlation has been found with hepatic inflammatory indices like transaminases

This result suggests that T3 concentration should be considered as a sensitive index of hepatic function in liver disease.

Green et al found normal FT3 and FT4 in a small group of cirrhotic patients while low FT4 and normal FT3 concentrations were present in alcoholic fatty liver.

Many studies performed on equilibrium dialysis, however showed decreased FT3 and normal or frequently increased FT4 concentration. These findings are confirmed by present study with direct radioimmunoassay of FT3 and FT4 in chronic liver disease.

These data suggest that in a patient with chronic liver disease, euthyroidism is maintained by a subtle equilibrium between low FT3 and increased FT4 concentrations

CONCLUSION

CONCLUSION

- The present investigation in which thyroid function has been evaluated with all the clinically available indices, confirms the existence of several abnormalities in thyroid function test in chronic liver disease, although showing that euthyroidism is maintained virtually in all patients, probably as a result of low normal FT3 and high normal FT4.

- Furthermore serum T3 concentration appear to parallel the severity of liver dysfunction

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Bianchi GP, Zoli M, Marchesini G, Volta U, Vecchi F, Iervese T, Bonazzi C, Pisi E. Thyroid gland size and function in patients with cirrhosis of the liver. Liver1991; 11:71–7.
2. L'age M, Meinhold H, Wenzel KW, Schleusener H. Relations between serum levels of TSH, TBG, T4, T3, rT3 and various histologically classified chronic liver diseases. J Endocrinol Invest1980; **3**:379–83.
3. Faber J, Thomsen HF, Lumholtz IB, Kirkegaard C, Siersbaek-Nielsen K, Friis T. Kinetic studies of thyroxine, 3,5,3'-triiodothyronine, 3,3,5'-triiodothyronine, 3',5'-diiodothyronine, 3,3'-diiodothyronine, and 3'-monoiodothyronine in patients with liver cirrhosis. J Clin Endocrinol Metab1981; **53**:978–84.
4. Guven K, Kelestimur F, Yucesoy M. Thyroid function tests in non-alcoholic cirrhotic patients with hepatic encephalopathy. Eur J Med1993; **2**:83–5.
5. Borzio M, Caldara R, Borzio F, Piepoli V, Rampini P, Ferrari C. Thyroid function tests in chronic liver disease: evidence for multiple abnormalities despite clinical euthyroidism Gut1983; **24**:631–6.
6. Huang MJ, Liaw YF. Clinical associations between thyroid and liver diseases. J Gastroenterol Hepatol1995; **10**:344–50.

7. Malik R, Mellor N, Selden C, Hodgson H. Characterising the effects of thyroid hormone on the liver: a novel approach to increase liver mass. Gut2000; **34** (Suppl. 1):78.
8. Van Thiel DH, Udani M, Schade RR, Sanghvi A, Starzl TE. Prognostic value of thyroid hormone levels in patients evaluated for liver transplantation. Hepatology1985; **5**:862–6.
9. Chopra IJ, Solomon DH, Chopra U, Young RT, Chua Teco GN. Alterations in circulating thyroid hormones and thyrotropin in hepatic cirrhosis: evidence for euthyroidism despite subnormal serum triiodothyronine. J Clin Endocrinol Metab. 1974 Sep;39(3):501–511.
10. Nomura S, Pittman CS, Chambers JB, Jr, Buck MW, Shimizu T. Reduced peripheral conversion of thyroxine to triiodothyronine in patients with hepatic cirrhosis. J Clin Invest. 1975 Sep;56(3):643–652.
11. Green JR, Snitcher EJ, Mowat NA, Ekins RP, Rees LH, Dawson AM. Thyroid function and thyroid regulation in euthyroid men with chronic liver disease: evidence of multiple abnormalities. Clin Endocrinol (Oxf). 1977 Dec;7(6):453–461.

12. Geurts J, Demeester-Mirkine N, Glinoer D, Prigogine T, Fernandez-Deville M, Corvilain J. Alterations in circulating thyroid hormones and thyroxine binding globulin in chronic alcoholism. Clin Endocrinol (Oxf). 1981 Feb;14(2):113–118.

13. Chopra IJ, Solomon DH, Hepner GW, Morgenstein AA. Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. Ann Intern Med. 1979 Jun;90(6):905–912.

14. Woeber KA, Maddux BA. Thyroid hormone binding in nonthyroid illness. Metabolism. 1981 Apr;30(4):412–416.

15. Chopra IJ, Teco GN, Nguyen AH, Solomon DH. In search of an inhibitor of thyroid hormone binding to serum proteins in nonthyroid illnesses. J Clin Endocrinol Metab. 1979 Jul;49(1):63–69.

16. Israel Y, Walfish PG, Orrego H, Blake J, Kalant H. Thyroid hormones in alcoholic liver disease. Effect of treatment with 6-n-propylthiouracil. Gastroenterology. 1979 Jan;76(1):116–122.

17. Larsen PR. Direct immunoassay of triiodothyronine in human serum. J Clin Invest. 1972 Aug;51(8):1939–1949.

18. Odell WD, Rayford PL, Ross GT. Simplified, partially automated method for radioimmunoassay of human thyroid-stimulating, growth, luteinizing, and follicle stimulating hormones. J Lab Clin Med. 1967 Dec;70(6):973–980.

19. Levy RP, Marshall JS, Velayo NL. Radioimmunoassay of human thyroxine-binding globulin (TBG). J Clin Endocrinol Metab. 1971 Mar;32(3):372–381.

20. Romelli PB, Pennisi F, Vancheri L. Measurement of free thyroid hormones in serum by column adsorption chromatography and radioimmunoassay. J Endocrinol Invest. 1979 Jan–Mar;2(1):25–40.

21. Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab. 1975 Jul;41(1):27–40.

22. Hepner GW, Chopra IJ. Serum thyroid hormone levels in patients with liver disease. Arch Intern Med. 1979 Oct;139(10):1117–1120.

23. Schussler GC, Schaffner F, Korn F. Increased serum thyroid hormone binding and decreased free hormone in chronic active liver disease. N Engl J Med. 1978 Sep 7;299(10):510–515.

24. L'age M, Meinhold H, Wenzel KW, Schleusener H. Relations between serum levels of TSH, TBG, T4, T3, rT3 and various histologically classified chronic liver diseases. J Endocrinol Invest. 1980 Oct–Dec;3(4):379–383.

25. Fischer JE, Baldessarini RJ. False neurotransmitters and hepatic failure. Lancet. 1971 Jul 10;2(7715):75–80.

26. Borzio M, Caldara R, Ferrari C, Barbieri C, Borzio F, Romussi M. Growth hormone and prolactin secretion in liver cirrhosis: evidence for dopaminergic dysfunction. Acta Endocrinol (Copenh*)*. 1981 Aug;97(4):441–447.

27. Scanlon MF, Pourmand M, McGregor AM, Rodriguez-Arnao MD, Hall K, Gomez-Pan A, Hall R. Some current aspects of clinical and experimental neuroendocrinology with particular reference to growth hormone, thyrotropin and prolactin. J Endocrinol Invest. 1979 Jul–Sep;2(3):307–331.

ANNEXURES

PROFORMA

Name Age Sex

O.P/ I.P No :

Occupation :

Address :

Per capita income :

Presenting complaints :

H/o present illness :

onset

duration

course

H/o suggestive of hypo- or hyperthyroidism

H/o associated symptoms

Past history :

H/o any jaundice/blood transfusions

Family history :

Personal history :

Diet :

Sleep :

Appetite :

Bowel & bladder habits :

Habits : smoking / alcoholism

H/o high risk behaviour

Menstrual history (in females):

Menarche/menopause; cycles; flow

Obstetric history (in females):

H/o pregnancy / lactation

H/o intake of OCPs

Treatment history :

H/o previous treatment / surgeries

General Physical Examination :

Consciousness; orientation

Built & nourishment

Febrile/afebrile

Pallor / cyanosis / clubbing / icterus / lymphadenopathy / pedal edema

Pulse rate : Peripheral pulses :

Blood pressure :

Respiratory rate :

Temperature :

Thyroid examination :

Systemic Examination :

Cardiovascular system :

Respiratory system :

Abdomen (including genital and per rectal examination):

Central nervous system :

DIAGNOSIS :

INVESTIGATIONS :

- Hb%, TC, DC, ESR, Platelet
- Urine – albumin, sugar, deposits
- Blood urea
- Serum creatinine
- Liver function tests
- Coagulation profile
- Ultrasound abdomen and pelvis
- Portal vein Doppler
- Serum T3, T4, TSH FT3, FT4
- Portal vein Doppler
- Ultrasonogram abdomen & pelvis
- CT abdomen (as required)

MASTER CHART FOR THE STUDY GROUP - CASES

S.No	Age	Sex	T3	T4	FT3	FT4	TSH	Bilirubin	Albumin	PT	SGPT
1	27	M	79.2	4.2	2.55	6.7	1.73	3.3	2.1	45	46
2	30	M	81.4	4.5	3.8	7.9	2.5	2.1	2.8	56	62
3	40	M	79	5.2	3.81	6.9	2.6	2	2.4	36	58
4	37	M	90.6	6	5.6	12.2	4.6	1.7	3.1	44	51
5	42	M	76.5	3.7	2.7	9	3.11	3.2	2	46	48
6	48	M	83	4.8	3.82	7.7	2.81	1.8	1.9	52	59
7	47	M	82.4	4	3.8	10.7	3.4	1.6	2.1	55	47
8	55	M	110.6	7.3	6.1	16.4	3.5	1.9	2.4	51	65
9	52	M	81.4	6.1	3.2	12	5	2.3	3	49	40
10	50	M	98.2	7	6	14	5.2	2	2.7	57	54
11	49	M	78	4.9	2.9	6.3	2.8	2.6	2	52	57
12	50	M	80	3.9	3.8	12.2	2.7	1.3	2.6	50	46
13	52	M	77	3.6	2.62	11.8	3.2	3	2.8	42	62
14	47	M	76	5.4	2.6	12.4	3.51	3.8	3.3	53	58
15	45	M	100.4	8.1	4.4	10.6	5.4	1.7	3.1	50	49
16	54	M	84	6.3	3.1	8.6	3.27	3.2	2.7	57	47
17	51	M	79	5.7	2.7	8.4	2.9	2.7	2.2	48	40
18	48	M	84.8	6.5	3.1	10.8	4.1	3.3	2.5	44	72
19	46	M	78.6	5.8	2.82	11.9	2.84	3.2	3	52	49
20	50	M	77.8	5.8	4	11.72	2.72	2.9	2.9	41	59

MASTER CHART FOR THE STUDY GROUP - CASES

S.No	Age	Sex	T3	T4	FT3	FT4	TSH	Bilirubin	Albumin	PT	SGPT
21	55	M	81.6	7.5	3.15	13.2	3.31	2.2	2.1	44	35
22	48	M	82.4	6.4	3.8	13	3.2	2	2.4	47	45
23	60	M	83.6	7.4	3.9	10.62	2.7	2.4	2.5	43	67
24	72	M	78.2	6.2	3.2	8	3	2.1	2	39	56
25	52	M	79.3	6.4	3.12	10.2	3.1	3.4	2.2	52	49
26	70	M	112.2	9.7	4.8	15.2	5.3	1.9	3.2	56	39
27	54	M	114	8.2	4.45	15	3.5	2	3	42	58
28	48	M	84.2	7.2	3.1	11.9	3.1	2.2	2	40	49
29	53	M	76	6	3	7.2	1.82	2.7	2.8	36	40
30	59	M	77.9	7.1	4.5	10	2	3	1.9	47	50
31	32	F	85.7	6.3	3.9	15.9	1.96	1.7	2	41	62
32	42	F	77.4	6.1	2.9	10.9	1.89	2.9	3	34	49
33	48	F	82.6	6.6	4.2	12.6	2.5	2.3	2.8	39	47
34	56	F	79.9	6.2	2.8	12.3	2.5	2.5	3	30	54
35	34	F	78.7	7	2.91	12.4	2	2.6	2.7	43	55
36	38	F	86.2	6.7	4.1	15.8	3.41	1.9	2.3	45	50
37	30	F	78.2	6.8	2.94	10.8	2.7	3	2.6	47	43
38	45	F	82.8	6.9	3.95	14	3.38	1.8	2.9	34	45
39	39	F	83.4	6.8	3.8	13.4	3.3	3.2	2.8	39	58
40	35	F	84	7.2	2.6	13.2	3.36	2.6	3	34	57

MASTER CHART FOR THE STUDY GROUP - CONTROLS

S.No	Age	Sex	T3	T4	FT3	FT4	TSH	Bilirubin	Albumin	PT	SGPT
1	28	M	84	5.4	3.95	14.4	2.4	0.9	4.7	21	23
2	32	M	90.2	8.2	3.8	13.7	3.2	1.1	3.2	24	19
3	39	M	94	8.2	3.82	12.4	4.2	1.2	3.3	30	16
4	37	M	96.9	7.3	3.9	8.9	4	0.9	4.2	30	21
5	40	M	97.2	7.9	4	15.5	3.2	1.1	3	25	30
6	46	M	100.4	9.4	4.41	10.8	4.1	0.7	4	28	31
7	46	M	92.6	5.4	5	15	5.42	1.2	3.7	17	32
8	54	M	94.1	7.4	3.4	10.2	5.5	0.7	3.6	15	34
9	51	M	83	8.4	6.4	9.8	4.32	0.9	4.1	19	23
10	52	M	94.2	8.7	4.2	16	3.9	1.3	3.2	21	19
11	47	M	97.6	6	4.9	10.2	3.2	1.1	3.9	24	39
12	49	M	104.2	7.2	4.3	9.7	3.14	0.8	4.9	22	15
13	52	M	84.3	6.4	3.7	15	3.72	1	4	29	28
14	45	M	86.2	7.5	4.23	9.9	5.48	1.2	4.2	30	19
15	47	M	94.7	7.2	3.7	16.24	4.8	0.7	4.8	24	36
16	52	M	91.8	8.1	4.6	12	2	0.8	4.1	30	17
17	54	M	108.4	5.8	4.2	9.7	2.62	1.1	3.7	28	35
18	49	M	93.8	7.4	4.29	12.5	3.4	0.9	3.9	30	20
19	47	M	88.4	6.9	4.28	12.4	3	0.9	5	23	27
20	50	M	92.2	6.3	4.2	15.2	3.75	1.2	4	29	28

MASTER CHART FOR THE STUDY GROUP - CONTROLS

S.No	Age	Sex	T3	T4	FT3	FT4	TSH	Bilirubin	Albumin	PT	SGPT
21	54	M	83.4	4.6	4.4	14.4	2.4	0.8	4	20	19
22	49	M	98.2	7	3.8	12	3	1	3.7	23	20
23	58	M	110.4	5.2	5	15.4	2.3	1.2	3.8	28	17
24	70	M	82	5.9	4.96	13.4	4.3	0.7	4.2	30	15
25	52	M	87.2	6.8	2.9	11.7	4.3	1.1	3	21	30
26	69	M	99.2	7	3.81	12.5	5.4	0.6	4.5	26	34
27	55	M	118	5.4	4.2	10	3.8	1.2	3	17	23
28	48	M	99.2	7.5	4.4	16.4	3.2	0.7	3.6	16	34
29	51	M	87.2	7.7	5.4	12.52	2.72	0.9	4.3	15	37
30	58	M	88	5.8	2.8	12.2	3.9	1	4.1	18	31
31	30	F	89.3	7.7	4.31	15.5	4.15	1.1	3.9	20	39
32	42	F	98.2	5.2	3.9	13.6	5.4	0.8	4.7	22	42
33	47	F	93.6	10.2	4.1	11.9	3.2	0.9	4.9	27	28
34	56	F	86.2	5	5.2	16.2	3.4	1.2	4.2	30	27
35	35	F	91.4	7.2	4.32	10.1	2.5	0.9	4	23	36
36	38	F	83.2	8.9	4.26	13.8	4	0.8	4.1	30	31
37	32	F	90	7.3	3.6	16.4	2.6	1	5	26	35
38	44	F	84	8	3.5	8.75	3	0.7	4.8	32	28
39	38	F	96.2	6.9	4.5	15	3.1	0.9	4.2	27	22
40	36	F	92.6	7.2	4.2	13.7	4.14	1.1	4.6	21	30